

# The Management of Heterotopic Pregnancy with Transvaginal Ultrasound-Guided Local Injection of Absolute Ethanol

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## Abstract

**Aims:** The aim of the study is to present five cases of heterotopic pregnancy (HP) patients who received transvaginal ultrasound-guided local injection of absolute ethanol (AE).

**Settings and Design:** This was a case series and literature review in Reproductive Medicine Center of the 105<sup>th</sup> Hospital of the People's Liberation Army.

**Materials and Methods:** Five primary infertile women who underwent assisted reproductive technology were diagnosed with HP and treated with local injection of AE (1.0–2.5 ml) under transvaginal ultrasound guidance. The size of intrauterine (IU) and ectopic sacs and the level of serum beta-human chorionic gonadotropin as well as pregnancy outcomes were monitored after treatment.

**Statistical Analysis Used:** Not applicable.

**Results:** Four of five cases presented with lack of Doppler flow in the injected area after AE injection. Meanwhile, IU pregnancy proceeded well after treatment and delivered a normal newborn. One case received emergency surgery 3 h after local injection of 2.5 ml AE because of the rupture of ectopic gestational sac (GS). An early abortion was identified 7 days after the surgery.

**Conclusions:** Transvaginal ultrasound-guided local injection of AE is an alternative nonsurgical treatment for HP, yet overdose injection of AE will increase the risk of ectopic GS rupture.

**Keywords:** Absolute ethanol, assisted reproductive technology, heterotopic pregnancy, transvaginal ultrasonography

## INTRODUCTION

Heterotopic pregnancy (HP) refers to the coexistence of an ectopic pregnancy (EP) together with an intrauterine (IU) gestation. The incidence of HP in natural conception is estimated to be 1 in 30,000.<sup>[1]</sup> However, following the widespread use of assisted reproductive technology (ART), the incidence of HP has increased approximately to 1 in 100.<sup>[2]</sup> Several hypotheses have been proposed to interpret the cause of HP including previous pelvic inflammatory disease, abnormal hormonal milieu, multiple embryos transfer (ET), large volumes of transferred medium, position of transferred embryos deeper than anticipated, and uterine contraction

induced from the process of ET, whereas the main cause is still unclear.<sup>[3]</sup>

Rupture of EP is a leading cause of pregnancy-related mortality in the first trimester.<sup>[4]</sup> It is essential to diagnose and treat EP as early as possible. Due to the improvement of transvaginal ultrasonography (TVUS) which refers to doctors pass a transducer into the vagina to obtain internal images, and serum beta-human chorionic gonadotropin ( $\beta$ -HCG) measurement, the detection of EP at early gestational age (GA) has become possible. Surgery and medical treatment are two therapeutic

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options for HP/EP.<sup>[5]</sup> Laparoscopic operation is a common surgery option which has been considered as invaluable both in diagnosis and treatment, but it still involves surgical and anesthetic risks to the mothers and their IU pregnancy. Therefore, no invasion medical treatments are proposed. Previous studies have demonstrated that most unruptured and live EP could be successfully managed through local injection of methotrexate (MTX)/potassium chloride (KCL) or in combination with systemic administration of MTX, with the benefits of no general anesthesia and less tubal damage.<sup>[6,7]</sup> However, the management of HP is more difficult and complicated than EP due to the desire to preserve the IU pregnancy. The toxic effects of MTX, even locally injection, may associate with spontaneous abortion and congenital abnormality of remaining fetus.<sup>[8]</sup> Furthermore, life-threatening neutropenia and febrile morbidity had been reported following MTX treatment to EP.<sup>[9]</sup>

To manage HP successfully and to avoid severe systematic complications and adverse effects on IU pregnancy, a novel mode of management with transvaginal ultrasound-guided local injection of absolute ethanol (AE) was employed in this study.

## MATERIALS AND METHODS

### Patients' characteristics

From 2014 to 2017, five patients diagnosed with HP after *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI)-ET or frozen-thawed ET received transvaginal ultrasound-guided local injection of AE at our center. The patients preferred no invasion management for the strong desire to preserve the IU pregnancy. Their condition had

been carefully examined as hemodynamically stable and no signs of active vaginal bleeding with the GA  $\leq 7$  weeks and unruptured ectopic gestational sac (GS). The basic characteristics of patients were listed in Table 1.

The level of serum  $\beta$ -HCG 14 days after ET ranged from 742.47 mIU/ml to 4066.00 mIU/ml. In case 1, an IU GS (37 mm  $\times$  23 mm) with the visible fetus heartbeat and an ectopic GS (22 mm  $\times$  8 mm) in the cervix with affluent surrounding Doppler flow and no visible fetus heartbeat were detected under TVUS 35 days after ET. The level of serum  $\beta$ -HCG was more than 5000.00 mIU/ml (no dilution of the serum sample). In case 2 and case 3, the size of IU GS was 19 mm  $\times$  14 mm and 29 mm  $\times$  14 mm respectively, while the size of ectopic GS was 15 mm  $\times$  8 mm in the right tube and 21 mm  $\times$  12 mm in the left tube respectively under TVUS detection on the day of 28 and 31 after ET. The fetus heartbeats of IU and EP were identified in both the cases, with the levels of serum  $\beta$ -HCG 38,800.00 mIU/ml and 70,164.00 mIU/ml, respectively. In case 4, an IU GS (30 mm  $\times$  15 mm) with fetus heartbeat and a right adnexal mass (19 mm  $\times$  17 mm) with fluid echo and fetus heartbeat were identified 35 days after ET. The level of serum  $\beta$ -HCG was 224,977.00 mIU/ml [Figures 1 and 2]. In case 5, an IU GS (24 mm  $\times$  16 mm) and an ectopic GS (14 mm  $\times$  12 mm) in the right tube were identified with fetus heartbeats in both sacs 31 days after ET. The level of serum  $\beta$ -HCG was 166,063.00 mIU/ml.

### The procedure of transvaginal ultrasound-guided local injection of absolute ethanol

All the risks and benefits were informed to the patients before the treatment. The risks of sclerotherapy with AE

**Table 1: Characteristics of women with heterotopic pregnancies**

Case	Age (years)	History	Gravity/parity	Mode of ART	Number of embryos transferred	$\beta$ -HCG level 14 <sup>th</sup> day after ET (mIU/mL)	GA at diagnosis of HP (weeks)	Ectopic location	EP fetal heart beat	AE local injection (ml)	Other comments	Pregnancy outcome
1	26	Chronic salpingitis and left tubal obstruction	G0P0	IVF-ET	2	742.47	7	Cervix	-	2.0	-	Premature male infant
2	23	Bilateral tubal obstruction	G0P0	FET	2	824.58	6	Right fallopian tube	+	1.0; 2.0 (second injection)	Requiring second injection	Full-term live male infant
3	27	Laparoscopic operation for pelvic adhesion	G0P0	ICSI-ET	2	974.12	6+3	Left fallopian tube	+	1.5	-	Full-term live female infant
4	27	Laparoscopic operation for right ovarian cyst	G0P0	IVF-ET	2	825.66	7	Right adnexa area	+	1.5	-	Full-term live male infant
5	27	Bilateral tubal obstruction	G0P0	FET	2	4066.00	6+3	Right fallopian tube	+	2.5	Surgery for ruptured ectopic GS	Early abortion

ET: Embryo transfer, HP: Heterotopic pregnancy, EP: Ectopic pregnancy, AE: Absolute ethanol, ART: Assisted reproductive technology,  $\beta$ -HCG: Beta-human chorionic gonadotropin, FET: Frozen-thawed embryo transfer, IVF: *In vitro* fertilization, ICSI: Intracytoplasmic sperm injection, GS: Gestational sac, GA: Gestational age, +: EP with fetal heart beat, -: EP without fetal heart beat

are as followings: survived EP GS might need to repeat injection of AE; ruptured ectopic GS during or after treatment requires emergency surgical intervention; and an inadvertent puncture into blood vessels in the vicinity of the ectopic GS could cause severe internal hemorrhage. The benefits include the avoid of surgery and general anesthesia and no need for hospitalization as well as less cost. All the patients had been provided informed consent after counseling. All the operations were performed by a chief physician. The study was approved by the Reproductive Medical Ethics Committee of the 105<sup>th</sup> Hospital of the People's Liberation Army (Approval No.2014A012 was obtained on 1<sup>st</sup> February in 2014).

The vulva and vagina were prepared with sterile saline solution, and then, a 17G needle (Queensland, Australia) was used to puncture into the ectopic GS under TVUS guidance (GE Logiq 5 PRO, Gyeonggi, Korea). After suctioning the contents of the GS, 1.0 ml–2.5 ml AE was injected into GS based on the size of GS and the volume of the contents suctioned. The whole time of this procedure took <10 min without anesthesia. After injection of AE, a high-intensity image in injected site was observed under transvaginal ultrasound. All patients were monitored for 3 h after the procedure.

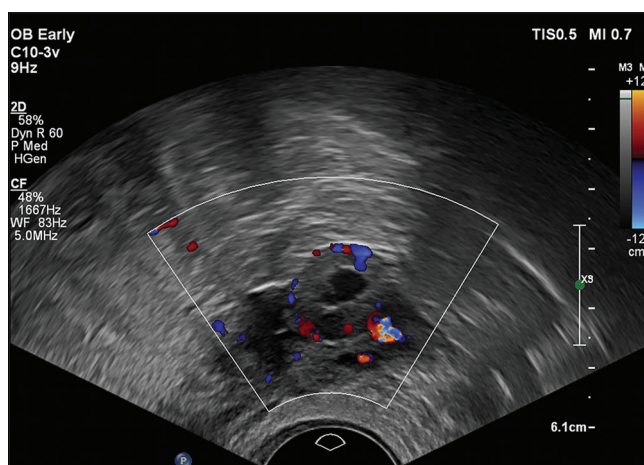
## RESULTS

All the patients tolerated the procedure well. In cases 1–4, the size of ectopic GS shrank or disappeared and a high-intensity image in the injected site was observed. No fetal heartbeat was visualized on the 3<sup>rd</sup> day postoperation. The follow-up was done for several weeks after injection until no Doppler flow and expansive sign of ectopic GS were identified [Figure 3].

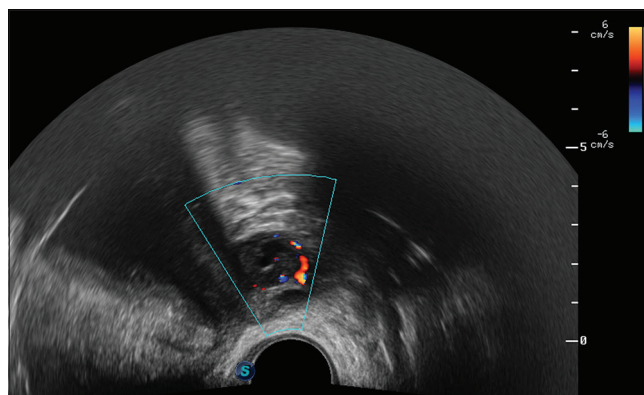
In case 1, the ectopic GS shrank from 22 mm × 8 mm to 21 mm × 6 mm 1 week later and 11 mm × 4 mm 3 weeks later, while the IU GS expanded from 37 mm × 23 mm to 45 mm × 39 mm 1 week after the treatment, and a premature male infant weighing 1500 g delivered vaginally at 30 weeks of gestation. In case 2, the ectopic GS expanded from 15 mm × 8 mm to 35 mm × 11 mm without fetal heartbeat, and the IU sac increased from 19 mm × 14 mm to 39 mm × 18 mm 2 weeks after the treatment. Serum level of  $\beta$ -HCG was 130,200.00 mIU/ml. Re-injection of 2.0 ml AE at the same location was performed. One week later, the ectopic GS shrank to 26 mm × 22 mm with the serum level of  $\beta$ -HCG 166,280.00 mIU/ml, and no re-expansion identified afterward. Meanwhile, the remaining IU pregnancy proceeded well, and a healthy male infant weighing 4050 g delivered at 38 + 5 weeks of gestation through the cesarean section. In case 3, the ectopic GS shrank from 21 mm × 12 mm to 16 mm × 12 mm, while the IU sac expanded from 29 mm × 14 mm to 36 mm × 19 mm



**Figure 1:** Transvaginal ultrasonography of an intrauterine gestation (left) coexisting with an ectopic gestational sac as an adnexal mass with fluid echo (right) before treatment



**Figure 2:** Transvaginal ultrasonography of a right adnexal mass with fluid echo and affluent Doppler flow around and visible fetus heartbeats before treatment



**Figure 3:** Transvaginal ultrasonography of a right adnexal mass with scanty Doppler flow around without fetus heartbeats 3 days after treatment

with the serum level of  $\beta$ -HCG 113,208.00 mIU/ml 1 week after the treatment, and a healthy female infant weighing 2050 g delivered at 38 weeks of gestation through the cesarean



section. In case 4, the right adnexal mass (19 mm × 17 mm) decreased to 16 mm × 14 mm, while the IU sac increased from 30 mm × 15 mm to 43 mm × 18 mm with the serum β-HCG level 255,925.00 mIU/ml 1 week after the treatment, and a healthy male infant weighing 3200 g delivered at 40 + 3 weeks of gestation through the cesarean section. In case 5, the patient felt severe lower abdominal pain and dizziness with abdomen muscle tension and tenderness 2.5 h after the treatment, and her vital signs were as followings: pulse – 108/min; blood pressure – 70/46 mmHg; erythrocyte – 2.75 × 10<sup>12</sup>/L; hematocrit – 24.30%; and hemoglobin – 86.0 g/L. Ultrasonography scan identified a large amount of hemorrhagic fluid in the abdominal cavity. Rupture of EP and hemorrhagic shock were diagnosed, and laparoscopic surgery was performed at once. An estimated 2300 ml blood was identified in the abdominal cavity with an active bleeding point in the right tube. The ruptured right tube was resected, and 1100 ml autologous blood was reinfused into the body. After the surgery, the patient recovered well, the remaining IU sac expanded to 29 mm × 17 mm with the visible heartbeat 4 days later, and then, the patient was discharged. Unfortunately, early abortion of IU pregnancy was identified 7 days after the surgery.

No malformations were diagnosed in all four born babies, and their physical and psychomotor developments were followed up after birth. The baby of case 1 weighed 11.2 kg with 85 cm in height, while case 2 baby weighed 12.3 kg with 89 cm in height at 2 years of age. The baby of case 3 weighed 9.3 kg with 75 cm in height at 1 year of age, and the case 4 baby weighed 4.3 kg with 53.8 cm in height 1 month after birth. Their height and body weight were comparable to the children conceived naturally in China.<sup>[10]</sup>

## DISCUSSION

HP was first reported by Duverney in 1708,<sup>[11]</sup> during an autopsy on a patient who had died of a ruptured EP. Early diagnosis is the key to manage HP but remains many challenges. It is acknowledged that patients with symptoms such as abdominal pain, vaginal bleeding, and rectal tenesmus might be diagnosed earlier than those without symptoms.<sup>[12,13]</sup> However, these

symptoms are rarely seen in HP due to the coexistence of IU pregnancy. Transvaginal ultrasonography has been considered as a valuable tool in early diagnosis of HP. However, GS might be mistaken with a hemorrhagic corpus luteum or ovarian cyst for the patients who underwent ART.<sup>[14]</sup> Persistent enlargement of adnexal fluid mass with affluent blood flow may be the early ultrasonographic sign of EP. Therefore, even when an IU pregnancy is diagnosed, transvaginal ultrasonic scan should be carefully carried out to rule out HP in ART patients. In our center, the first transvaginal ultrasonography was usually performed on 30–35 days after ET. In this study, all five HP patients were diagnosed HP within 7 weeks of gestation.

The managements of HP mainly include surgery and medical treatment, while the choice remains controversial due to the desire to preserve the IU pregnancy. Local injection medicines such as MTX into EP have been demonstrated successful in managing EP or cesarean scar ectopic pregnancy,<sup>[15]</sup> with the advantages of being simple, effective, less invasive, and inexpensive, although a combination with systemic MTX administration was needed sometimes.<sup>[5]</sup> MTX not only can lead to embryonic development arrest but also has various side effects on the mother such as bone marrow suppression, liver enzyme elevation, rash, alopecia, and stomatitis.<sup>[14]</sup> Therefore, MTX has little value in HP management for its toxic effects on both mother and IU fetus.<sup>[16]</sup> Other medicines such as KCL and hyperosmolar glucose were also reported in managing HP for avoiding the potential systemic side effects and toxicity to IU pregnancy.<sup>[17,18]</sup> However, a case report revealed that the therapeutic effect of KCL might not satisfactory for two of three cases abortive after local injection of KCL, suggesting that KCL might also have adverse effects to IU pregnancy.<sup>[19]</sup> Studies carried out on the management of heterotopic/EP through local injection are listed in Table 2.

Laparoscopy and transvaginal ultrasound guidance are two common methods for the local administration of drugs. It had been confirmed that direct intraocular injection under ultrasound guidance was superior to the laparoscopically controlled “blind” intratubal injection.<sup>[24]</sup> Furthermore, the latter needs carbon dioxide pneumoperitoneum and

**Table 2: Summary of studies on the management of heterotopic/ectopic pregnancy through local injection**

Author, years of publication	Number of patients	Mean age (year)	Agent	Type	Dosage	Volume
Feichtinger and Kemeter, 1987 <sup>[15]</sup>	1	29	MTX	EP	10 mg	1 ml
Scheiber and Cedars, 1999 <sup>[2]</sup>	1	37	KCL	HP	2 mmol/2 ml	4 ml
Kaijima et al., 2006 <sup>[20]</sup>	69	35	AE	EP	0.3 ml	0.3 ml
Chen et al., 2011 <sup>[21]</sup>	17/11	30/31	Etoposide/MTX	EP	50 mg	-
Ugurlucan et al., 2012 <sup>[22]</sup>	1	34	KCL	HP	2 mEq/ml	2 ml
Allison et al., 2012 <sup>[17]</sup>	1	31	Hyperosmolar glucose	HP	50%	Equal with aspirated
Ishikawa et al., 2016 <sup>[23]</sup>	11	31	Diluted vasopressin	EP	4–10 units	-

MTX: Methotrexate, KCL: Potassium chloride, AE: Absolute ethanol, HP: Heterotopic pregnancy, EP: Ectopic pregnancy

general anesthesia, which may have an adverse effect on IU pregnancy.<sup>[25]</sup>

AE is a dehydrating agent which could quickly infiltrate into the chorionic tissue surrounding the GS and then dehydrate and destroy chorionic villi. In 2006, Kajijima *et al.*<sup>[20]</sup> first reported this novel management for the patients with EP and found that the serum level of  $\beta$ -HCG decreased 10%–30% within 2 h after the local injection of AE, quicker than MTX (2–3 days). Moreover, patients' financial burdens are alleviated since AE costs less. Some prospective clinical studies had demonstrated that the local injection of AE for the patients with hydrosalpinx could improve the outcomes of IVF with no adverse effect on ovarian reserve and perinatal outcomes.<sup>[26,27]</sup> However, local injection of AE for EP was usually carried out at an early stage of GA (5-week gestation age), and the serum  $\beta$ -HCG level was <4000 mIU/mL without fetus heartbeat.<sup>[20]</sup> Furthermore, the candidates should be hemodynamically stable without the sign of ectopic GS rupture and no contraindications to the agent furthermore, patients should be followed up strictly after the operation and emergency surgery is necessary once there are signs of ectopic GS rupture.

In this study, gestation age of five cases was 6–7 weeks with the level of serum  $\beta$ -HCG ranged from 38,800.00 mIU/ml to 224,977.00 mIU/ml when local injection of AE was carried out, and the size of ectopic GS ranged from 15 mm  $\times$  8 mm to 19 mm  $\times$  17 mm and visible fetus heartbeats in four cases. Four cases who received local injection of AE delivered healthy live birth, and the babies' physical and psychomotor developments were in the normal range of children conceived naturally in China,<sup>[10]</sup> indicating that the management of HP with transvaginal ultrasound-guided local injection of AE may not have adverse effects on the IU pregnancy and could be efficiently carried out within 7 weeks of GA.

The dose and concentration of agents are important for effectiveness and safety when medical treatment was carried out. In this study, the dose of AE administrated in four successful cases was all within 2.0 ml, whereas one case received emergency laparoscopic surgery for rupturing of EP when 2.5 ml AE was injected into ectopic GS, suggesting that local injection of overdose AE may lead to a higher risk of ectopic GS rupture. It was also found that the ectopic GS in one case enlarged 2 weeks after injection 1.0 ml AE. After additional injection of 2.0 ml AE being performed, the ectopic GS decreased from 35 mm  $\times$  11 mm to 26 mm  $\times$  22 mm 1 week later, and no re-expansion and any complication identified afterward. Therefore, the management of HP with transvaginal ultrasound-guided local injection of AE should be carried out in a limited volume (<2.0 ml). If it does not work efficiently, additional injection could be performed. The main limitation of this study is small sample size. In addition,

the valid dose and opportunity of AE administration and its effectiveness and safety remain further evaluation through a large randomized controlled trial.

## CONCLUSIONS

Transvaginal ultrasound-guided local injections of AE might be served as an alternative option for the management of unruptured HP at a very early stage, with the advantage of less invasive and expensive.

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## Conflicts of interest

There are no conflicts of interest.

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